HHS Public Access

Author manuscript

Curr Opin Hematol. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

Curr Opin Hematol. 2022 January 01; 29(1): 34–43. doi:10.1097/MOH.0000000000000692.

Diverse functions of long non-coding RNAs in AML: emerging roles in pathophysiology, prognosis, and treatment resistance

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Abstract

Purpose of review: Advancements in the next-generation sequencing technologies have identified rare transcripts of long non-coding RNAs (lncRNAs) in the genome of cancers, including in acute myeloid leukemia (AML). The purpose of this review is to highlight the contribution of lncRNAs in AML pathogenesis, prognosis, and chemoresistance.

Recent findings: Several studies have recently reported that deregulated lncRNAs are novel key players in the development of AML and are associated with AML pathophysiology and may serve as prognostic indicators. A few aberrantly expressed lncRNAs that correlated with the recurrent genetic mutations in AML such as *NPM1* and *RUNX1* have recently been characterized. Moreover, a few lncRNAs in *MLL*-rearranged leukemia have been described. Additionally, the involvement of lncRNAs in AML chemoresistance has been postulated.

Summary: Investigating the functional roles of the non-coding regions including lncRNAs, may provide novel insights into the pathophysiology, refine the prognostic schema, and provide novel therapeutic treatment strategies in AML.

Keywords

Acute myeloid leukemia; lncRNAs; *NPM1* ; *RUNX1* ; *FLT3*-ITD; *MLL* ; chemoresistance

Introduction

Acute myeloid leukemia (AML) is characterized by an expansion of the abnormal myeloid progenitor cells in the bone marrow and blood resulting from differentiation block (1). Research in AML has traditionally been protein-centric but is now evolving as the involvement of transcripts from the non-coding genome in disease pathogenesis has emerged in recent literature. High throughput analyses demonstrate that human genomes are actively transcribed to produce thousands of lncRNAs that do not encode for functional proteins (2). LncRNAs are arbitrarily defined as RNA transcripts of more than 200 nucleotides in length, transcribed by RNA-polymerase II, which may undergo splicing and polyadenylation (2)

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Conflicts of interest: None

(3). LncRNAs exhibit poor sequence conservation across different species but demonstrate higher tissue and development-specific expression than the mRNAs (4). Interestingly, lncRNAs can bind to the DNA, RNAs, and proteins, thereby regulating diverse cellular processes (5). While the number of functional lncRNAs is still debated, it is well established that lncRNAs have important roles in both physiological development and pathological conditions, including cancer initiation, progression, and chemoresistance (5) (6). Figure 1. Illustrates a general overview of lncRNAs' mechanism(s) that have been reported in AML up to now.

In this review, we first discuss lncRNAs in AML pathogenesis and their prognostic significance. Next, we discuss recently characterized lncRNAs that are associated with recurrent mutations in AML including *NPM1, RUNX1, FLT3*-ITD, and *DNMT3A* (Table 1). This is followed by a concise discussion on novel lncRNAs involved in *MLL*-rearranged leukemia (Table 1). Lastly, we discuss lncRNAs involved in AML chemoresistance (Fig. 2, Table 2).

LncRNAs as potential risk stratification biomarkers in AML

Extensive profiling studies have been a popular strategy to identify distinct lncRNAs associated with AML prognosis and pathogenesis. Several recent studies demonstrated the potential roles of lncRNA signatures in AML risk stratification for patients across a diverse age range. For instance, a combined signature of 48 lncRNAs and 24 lncRNAs can predict the treatment response in older and younger cytogenetically normal AML (CN-AML) patients respectively (7) (8). Mer et al. utilized an RNA-seq based lncRNA profiling of 274 AML patients and the findings were subsequently validated in a TCGA-AML cohort. The authors identified 33 individual lncRNAs associated with overall survival (OS). Based on lncRNAs' expression, the authors classified all the patients into four distinct molecular subtypes. Remarkably, these lncRNAs-driven subtypes lacked high concordance with any of the conventional genetic or clinical factors or mRNA-based subtypes, suggesting that lncRNAs-subtypes provide independent prognostic information (9). A few studies took a more quantitative approach and formulated a lncRNA scoring system to predict OS and disease-free survival (DFS) in AML, and responses to allogeneic stem cell transplant (10). Relapse after treatment is common in AML. It occurs in 40–50% of younger and even higher in the elderly patients (11). One recent study highlighted the values of lncRNAs' expression signatures in the prediction of relapse in adult CN-AML patients. Walker et al identified a 10-gene expression signature that is predictive of relapse in CN-AML patients and these are independent of the mutations that are known to impact the outcome in AML, including 3 lncRNA genes (12). The observations from these risk stratification studies await further validation using larger, independent cohorts, but they suggest that perhaps the use of lncRNA signatures could augment the current standard of AML risk stratification based on patient demographics, chromosomal abnormalities, and mutation status. Studies using RNA-seq also demonstrated the intriguing roles of recurrent genetic variants in nucleotide sequences of lncRNAs in AML, although their functional significance awaits further investigation (13).

Association between lncRNAs and recurrent mutations in AML provide mechanistic insights

The interesting observations of the potential prognostic values of lncRNA in AML raise the question of the underlying mechanisms of such associations. While the precise mechanistic roles of many lncRNAs associated with AML remain unknown, we do know a great deal about the mechanisms of master regulators of haematopoiesis and the consequences of their mutations through decades of research. Examples of such regulators include NPM1, RUNX1, FLT3, TET2, DNMT3A, and MLL. Investigating lncRNA associated with mutations in these hematopoietic regulators can provide insights and directions for further investigation of lncRNA's involvement in AML pathophysiology.

Nucleophosmin (*NPM1*) associated lncRNAs

NPM1 plays important and multifaceted roles in hematopoiesis and is frequently mutated in AML. Nearly 20%−30% of newly diagnosed AML patients harbor *NPM1* mutation (14). Aberrant Homeobox (*HOX*) expression has been linked to *NPM1* mutation in AML (15). The *HOXA* and *HOXB* genes are upregulated in *NPM1* mutated AML compared to the wild-type *NPM1* (16). The mutant NPM1 protein is abnormally localized in the cytoplasm and is recently reported to maintain the leukemic state through *HOX* expression (17). While a few lncRNAs embedded in the *HOX* gene loci are reported to participate in cancer pathogenesis by regulating the expression of the protein-coding *HOX* genes (eg. *HOTAIR, HOTTIP*) (18,19), others like *HOXB-AS3* do not impact the *HOX* gene expression and function via other mechanisms (20). This section of the review will highlight recently reported, NPM1-associated lncRNAs that are located at the *HOX* gene loci, *HOXB-AS3*, and *HOXBLINC*, as well as lncRNAs that are outside the *HOX* gene loci.

HOXB-AS3

HOXB-AS3 is upregulated in CN-AML patients with *NPM1* mutation. RNA-seq analysis revealed that the expression of *HOXB-AS3* in *NPM1*mut patients (n=223) was approximately three-fold higher than wild-type *NPM1* patients (n=120). Knockdown of *HOXB-AS3* in OCI-AML3 (*NPM1*mut AML cell line) led to a decrease in the number of cells in the S-phase as well as a decrease in colony-forming capacity. Reduced expression of *HOXB-AS3* also prolonged the survival of xeno-transplanted mice. Mechanistically, *HOXB-AS3* interacts with ErbB3-binding protein 1 (*EBP1*) that can interact with *NPM1* in the nucleus to regulate the transcription of rRNA. Thus, *HOXB-AS3* guides *EBP1* to the rDNA locus and modulates EBP1-NPM1 complex formation which in turn maintains the proliferative phenotype in AML (20). Moreover, higher expression of *HOXB-AS3* has also been reported to be an adverse prognostic marker for de novo AML patients as well as primary MDS patients (21).

HOXBLINC

Another lncRNA located at the anterior of *HOXB* gene locus named *HOXBLINC* promotes hematopoietic development by upregulating *HOXB* gene expression via recruitment of SETD1A/MLL histone H3K4 methyltransferases complexes (22). More recently, *HOXBLINC* was found to be upregulated in AML patients with *NPM1* mutation as well

as in AML cell lines that carry *NPM1* mutation (OCI-AML3 and IMS-M2). Downregulation of *HOXBLINC* in OCI-AML3 cells significantly decreased cell viability, induced apoptosis, and impaired the transcription of mutant *NPM1* (NPM1c+) signature genes like *MEIS1* and *RUNX1*. Moreover, RNA-seq analysis of wild-type LSK cells versus LSK cells derived from *NPM1* mutant knock-in ($NPM1^{c/+}$) mice showed upregulation of *HOXBLINC* as well as some other signature genes associated with NPM1c+ like *MEIS1* and *RUNX1*. The authors further demonstrated that *HOXBLINC* mediates long-range chromatin interactions to drive the target genes' regulatory networks in HSPCs. Consistent with the previous study, *HOXBLINC* was shown to recruit *SETD1A* and *MLL*. Furthermore, recruitment of *MLL1* (and not SETD1A) appears to be the key in *HOXBLINC* overexpression-mediated leukemogenesis (23). This observation was consistent with a previous study suggesting that chromatin binding of *MLL1* is crucial for *NPM1* mutated leukemias (24). However, how *HOXBLINC* is upregulated in NPM1c+ AML remains unknown.

Outside of the *HOX* gene locus, a few other lncRNAs associated with *NPM1*-mutation in AML have been well characterized in terms of their potential pathogenic mechanisms, including lncRNA overexpressed in *NPM1*-mutated AML patients (*LONA*) and lncRNA Colorectal Neoplasia Differentially Expressed (*CRNDE*)

LncRNA overexpressed in *NPM1*-mutated AML patients (*LONA*)

Clara et al. performed RNA-seq on a cohort of 40 AML patients and found 12 distinct lncRNAs that are differentially expressed in wild-type versus mutant *NPM1* AML patients (25). In the process of further characterization of these lncRNAs, *LONA* emerged as a novel lncRNA hypothesized to play a critical role in AML pathogenesis through *NPM1*. *LONA* switches its subcellular localization from being cytoplasmic in the wild-type *NPM1* AML cells to becoming nuclear in *NPM1*-mutant AML as the mutant *NPM1* is exported in the cytoplasm. Interestingly, knockdown of *LONA* enhanced Cytarabine (Ara-C)-triggered apoptosis irrespective of the mutational status of *NPM1* as evidenced in OCI-AML3 (NPM1-mut) and OCI-AML2 (NPM1-wt) cells. Overexpression of *LONA* lncRNA reduced the survival of transplanted NOD scid gamma (NSG) mice but did not impact OCI-AML3 cells. Furthermore, manipulation of *LONA* followed by RNA-seq identified proteins involved in myeloid differentiation such as *HSB1*, *MAFB*, and *ASB2* as major targets of *LONA* lncRNA. Taken together, Gourvest et al. reported that the oncogenic functions of *LONA* lncRNA are through a nucleocytoplasmic cross-transport between mutant *NPM1* and *LONA* lncRNA (26).

lncRNA Colorectal Neoplasia Differentially Expressed (*CRNDE*)

High expression of *CRNDE* in AML patients was first reported by Wang et al.(27). The authors demonstrated that knockdown of *CRNDE* decreased the cell viability and increased apoptosis in U937 cells. More recently, a strong correlation between the expression of *CRNDE* and *NPM1* mutations in AML has been reported. Knockdown of *CRNDE* in OCI-AML3 cells could promote differentiation as evidenced by the increase of CD11b in *CRNDE* depleted AML cells. Similar inhibitory effects were also observed when *CRNDE* was downregulated in FAB M3 AML cells-NB4. Mechanistically, the authors demonstrated that *CRNDE* promotes leukemogenesis by sponging miR-181 and modulating the NOTCH

signaling pathway in acute promyelocytic cells (28). However, the precise functional roles of *CRNDE* in *NPM1* mutated AML remains unclear. Recently, Hola et al. conducted qRT-PCR based expression analysis of *CRNDE* from the diagnostic blood samples of 200 de novo adult AML patients compared to 50 healthy control samples, which revealed that upregulation of *CRNDE* was an adverse independent prognostic marker for complete remission in CN-AML patients (29).

RUNX1-associated lncRNAs

Runt-related transcription factor 1 (RUNX1) is a master regulator of hematopoiesis and is crucial for defining the definitive hematopoietic stem cell (30). It is found to be frequently mutated in a variety of hematological malignancies (31). The *RUNX1* gene is involved in several chromosomal translocations in leukemia. The most common chromosomal translocation is the t (8;21) which produces a RUNX1-ETO chimeric protein and is found in 30%−40% of FAB-M2 AML patients (32). This section of the review will highlight recently reported *RUNX1* associated lncRNAs that have been characterized in AML, including *CASC15, and LOUP*.

CASC15

Another study by Fernando et al. found upregulation of lncRNA cancer susceptibility candidate 15 (*CASC15)* in pediatric AML patients with the t (8;21) translocation and in B-cell acute lymphoid leukemia (B-ALL) patients with the t (12;21) translocation. The authors demonstrated that *CASC15* affects the expression of its neighboring oncogene-*SOX4*, by regulating the Yin and Yang-1 (YY1) transcription factor (33). Thus, this is an example demonstrating that lncRNAs can recruit transcription factors and affect gene expression. Notably, although *CASC15* is upregulated in *RUNX1*-translocated leukemia, the mechanism of its action was found to be independent of RUNX1.

LOUP

Trinh et al. have identified a novel lncRNA-Long noncoding RNA originating from the upstream regulatory element (URE) of *PU.1* (also known as Spi-1), named as *LOUP* that mediates active chromatin loop formation at *PU.1* locus which is critical for *PU.1* expression.

PU.1, a major downstream target of *RUNX1*, is a hematopoietic lineage-specific ETS-family member and its downregulation is reported to vitiate myeloid cell differentiation leading to AML (34) (35) (36). *PU.1* expression is impeded by RUNX1-ETO (AML with t (8;21) translocation) but the precise mechanism of this inhibition is unclear (37). Trinh et al. identified a spliced, and polyadenylated lncRNA-*LOUP* that was expressed exclusively in the myeloid cells. Depletion of *LOUP* in U937 cells increased the cell proliferation and decreased the expression of a myeloid marker, CD11b. Interestingly, *LOUP* expression was correlated with *PU.1* expression, and knockdown of *LOUP* also depleted *PU.1* mRNA levels. Previous studies have shown that the formation of chromatin looping facilitated by the URE and proximal promoter (PrPr) interaction is required for PU.1 induction (34) (38). In this study, the authors demonstrated that at the PU.1 locus, *LOUP* mediates the chromatin loop formation by recruiting RUNX1 to the RUNX1-binding motifs at both the URE and

the PrPr. Interestingly, *LOUP* and *PU.1* were downregulated in AML patients with t (8;21) translocation as compared to AML patients with normal karyotype. Last, RUNX1-ETO was demonstrated to inhibit *LOUP* transcription by deacetylating thereby restricting the promoter accessibility (39).

LncRNAs associated *FLT3*-ITD, *TET2*, and *DNMT3A* mutations

About 30% of AML cases have mutations in the Fms-like tyrosine kinase 3 (*FLT3*) gene. The more frequent internal tandem duplication (ITD) mutation in the juxtamembrane domain is found in 25% of AML cases while point mutation or deletion in the tyrosine kinase domain (TKD) is found in about 7%−10% of AML cases (40). Also, the genes involved in DNA methylation including ten-eleven translocation 2 (*TET2)* and DNA methyltransferase 3A (*DNMT3A)* are frequently mutated in CN-AML patients (41). DNMT3A mutations occur in approximately 20% of AML cases and are independently associated with a poor outcome (41,42). In this section, we discuss some recently reported lncRNAs associated with *FLT3*-ITD, *TET2*, and *DNMT3A* mutations in AML.

MORRBID—*MORRBID*, a lncRNA specifically expressed in myeloid cells, has been previously shown to repress the pro-apoptotic gene *BIM* via a DNA loop formation *in cis* (43). Recently, higher expression of *MORRBID* was reported in AML patients with *TET2* mutation. Also, a three-fold increase in *MORRBID* expression was observed in patients with *FLT3*-ITD mutation. To investigate the functional significance of *MORRBID* in AML, Cai et al. utilized a murine model of AML induced by loss of *TET2* and *FLT3*-ITD mutation (*TF* mice) and mutants of TF lacking *Morrbid* (*TFM* mice). Data from these models suggested that loss of *Morrbid* increased Bim expression and reduced the leukemic cell percentage in peripheral blood of *TFM* mice which prevented the infiltration of leukemic cells in the lungs of *TFM* mice, thus prolonging their survival (44).

SOCS2-AS

Overexpression of lncRNA suppressor of cytokine signaling-2 (*SOCS2-AS*) was associated with AML patients and cells harboring *FLT3*-ITD mutation. siRNA-mediated knockdown of *SOCS2-AS* in *FLT3*-ITD+ AML cells (Molm-13, MV4–11) decreased the cell viability and induced apoptosis. Also, decreased expression of STAT5/p-STAT5 was observed post knockdown of *SOCS2-AS*. Moreover, it was reported that *SOCS2-AS* could regulate genes of the STAT5 pathway by sponging miR221 (45).

Lastly, Yu et al. analyzed TCGA-LAML dataset and reported 619 differentially expressed (DE) lncRNAs as well as 1,428 DEmRNA genes in *FLT3*-ITD mutant samples versus *FLT3*-ITD WT samples. Interestingly, high expression of *SH3TC2-DT/SH3TC2* gene pairs was associated with *FLT3*-ITD mutation, high WBC count, intermediate genetic risk, and poor survival in AML. High expression of *SH3TC2-DT/SH3TC2* gene pair in *FLT3*-ITD mutants was also validated in the BeatAML dataset. Additionally, high expression of this gene pair also showed enrichment of transcripts related to stemness, quiescence, and leukemogenesis thereby hinting at a possible role in *FLT3*-mutant LSCs (40). However, further investigations are essential to confirm this hypothesis.

Analysis of differential gene expression in *Dnmt3a* R878H mutation conditional knock-in mice compared to WT mice identified 6 murine lncRNAs that were associated with *DNMT3A* mutation and poor prognosis. However, these lncRNAs were not conserved in humans and hence the expression of these murine lncRNAs could not be evaluated in human AML patients (46). A comprehensive evaluation of specific lncRNAs associated with *DNMT3A*-mutation is still awaited. Additionally, the expression of *HOTAIR* and *H19* positively correlates with *DNMT3A* mutated AML (47,48). However, their functional role in the leukemogenesis of *DNMT3A*-mutated AML is unexplored.

LncRNAs associated with mixed-lineage leukemia (*MLL*) gene rearrangements

Nearly 70% of infant leukemic patients and about 10% of adult AML cases are reported with rearrangement of mixed-lineage leukemia (*MLL*) gene (now renamed *Lysine [K]-specific MethylTransferase 2A* or *KMT2A*) by 11q23 translocation (49).

Recently, lncRNAs *HOXA10-AS* and *LAMP5-AS1* have been associated with *MLL*-rearranged leukemia.

LAMP5-AS1

LAMP5-AS1 was significantly upregulated in *MLL* leukemia patients (n=58) as compared to *MLL*-WT patients (n=163). Knockdown of *LAMP5-AS1* in the primary *MLL* CD34+ leukemic cells inhibited the self-renewal capacity and increased differentiation in the cells. Also, similar data were obtained from the xenograft models. Mechanistically, *LAMP5-AS1* was demonstrated to interact and enhance the enzyme activity of a histone methyltransferase-disruptor of telomeric silencing 1-like (DOT1L) in *MLL* leukemia (50). In summary, the high expression of *LAMP-AS1* in *MLL* leukemia helps to maintain high methyltransferase activity of DOT1L and global H3K79 methylation thereby upregulating transcription of DOT1L target genes, including genes involved in the self-renewal.

HOXA10-AS

HOXA10-AS is an HSC-specific lncRNA and it is upregulated in various *MLL*-rearranged AML cell lines. Knockdown of *HOXA10-AS* reduced the number of cells in the S-phase and induced apoptosis in AML cells. In contrast, the overexpression of *HOXA10-AS* in CD34+ HSPCs significantly impaired monocytic differentiation. Mechanistically, the authors demonstrated that *HOXA10-AS* acted in *trans* via upregulating the target genes of the *NF- kB* pathway (51).

Potential mechanisms of lncRNAs conferring drug resistance in AML: autophagy, cellular signaling, and microRNA sponging

Numerous studies support the hypothesis that deregulated lncRNAs can contribute to AML chemoresistance. In this section, we discuss some of the recently identified lncRNAs involved in chemoresistance in AML, especially those that act through leukemic stem cells (LSCs), regulate important cellular signaling pathways, and sequestering microRNAs (Fig. 2). Table 2 provides a summary of lncRNAs discussed in this review.

LSCs are an important subset of tumor cells involved in AML pathogenesis (52). The presence of LSCs has been proposed as a major cause of relapse in AML due to their self-renewal property. In this regard, two LSCs-associated lncRNAs- *DANCR* and *LINC00152*, have recently been investigated for their contribution to AML chemoresistance. *DANCR*, previously described as an LSC-associated lncRNA based on RNA-seq profiling studies, was found to be upregulated in AML cells treated with Ara-C. Knockdown of *DANCR* in LSCs led to a decrease in stem-cell renewal capacity, and in vivo targeting of *DANCR* increased the survival of mice after serial transplantation (53). Moreover, the overexpression of *DANCR* confers while siRNA-mediated depletion decreases the Ara-C resistance in human AML cell lines. The induction of autophagy is a mechanism utilized by cancer cells to gain resistance to the anti-cancer drugs (54). *DANCR* promoted autophagy in Ara-C treated AML cells by sponging miR-874–3P, which in turn upregulated the expression of *ATG16L1*, a critical component in autophagy and is associated with multiple-drug resistance in solid tumors (55). *LINC00152* was highly expressed in CD34+ LSCs in AML patients. The expression of *LINC00152* was correlated with 15 genes within a cluster of 17-gene biomarkers that would accurately predict chemoresistance in AML. Interestingly, knockdown of *LINC00152* reduced chemoresistance in K562 cells. Moreover, the expression of *LINC00152* was correlated with poly (ADP-ribose) polymerase 1 (*PARP1*) expression and knockdown of *LINC00152* resulted in decreased *PARP1* expression which consequently resulted in an increased sensitivity of AML cells to the DNA damaging agent-doxorubicin. Thus, *LINC00152* potentially contributes to the chemoresistance of LSCs in AML via upregulating PARP1 (56).

LncRNAs can affect various cell signaling pathways and contribute to chemoresistance. For example, lncRNA-*CRNDE* inhibits the Wnt/β-catenin pathway while *HOTAIR* promotes drug resistance partially via the AKT pathway. LncRNA-*CRNDE* was significantly upregulated in patients with Adriamycin (ADR) based chemotherapy. Notably, knockdown of *CRNDE* increased apoptosis, suppressed proliferation, and increased chemosensitivity of ADR-resistant AML cells. Moreover, the authors demonstrated that in ADR-resistant AML cells, *CRNDE* functions via inhibiting the Wnt/β-catenin pathway (57). Another lncRNA, *HOTAIR*, is overexpressed in AML and its expression is decreased post-treatment in AML patients (58). It is consistently reported to be correlated with shorter OS and DFS (47,58,59). It is known to mediate ADR resistance by regulating the expression of P21 and AKT/Notch1 signaling pathways in K562/A02 cells (60).

One emerging mechanism of how lncRNAs mediate chemoresistance is through sequestration of different miRNAs and regulating their target genes. LncRNAs *HOXA-AS2, TUG1, MALAT1, XIST, SNHG5*, and *KCNQ1OT1* are some of such examples, in addition to *DANCR* as described above. *HOXA-AS2* is overexpressed in AML tissues and cell lines (61), and it is upregulated in AML patients after ADR chemotherapy (62). The investigations on ADR-resistant AML cells demonstrated that *HOXA-AS2* sponges miR-520c-3p. Additionally, 100 calcium-binding protein A4 (S100A4) was found to be the downstream target of miR-520c-3p (62). S100A4 is overexpressed in the nuclear proteome of AML as compared to normal CD34+ cells and is important for AML survival (63). However, the role of S100A4 in AML chemoresistance remains unknown. Higher expression of lncRNA Taurine upregulated gene 1 (*TUG1*) has been

correlated with poor OS and lower complete response (CR) rates in AML patients (64,65). Recently, Li et al. showed that TUG1 was upregulated in ADR-resistant AML patients as compared to ADR-sensitive AML patients. Knockdown of *TUG1* could resensitize HL60/ADR cells to ADR by promoting ADR-induced apoptosis and overcome ADR resistance by epigenetically silencing miR-34a via recruiting EZH2 in AML (66). A negative correlation between *MALAT1* expression and miR-96 expression was observed in AML patients as compared to healthy controls. Hu et al. demonstrated that *MALAT1* sponges miR-96 and knockdown of *MALAT1* could enhance the sensitivity of ADR-resistant AML cells by upregulating miR-96 (67). Similarly, lncRNA *XIST, SNHG5, and KCNQ1OT1* mediate chemoresistance by modulating the miR-29a/myc, miR-32/DNAJB9, and miR-326/myc+miR-193a-3p/TSPAN-3 axis, respectively (68,69). Taken together, the current literature has accumulated evidence that lncRNAs could regulate drug resistance in AML via diverse mechanisms (Fig. 2).

Conclusion

Dysregulation of lncRNAs has been postulated as a key player in promoting leukemogenesis and drug resistance in AML. In this review, we summarized recent studies on lncRNAs that are associated with prognosis, mutational signatures, and drug resistance in AML. However, in-depth functional characterization of the majority of these lncRNAs is still lacking. Thus, dissecting the diverse mechanisms specifically shaped by lncRNAs, such as how they promote self-renewal or differentiation block, could be highly beneficial in elucidating novel therapeutic targets in the treatment of AML.

Financial support and sponsorship:

This work was supported by the Singapore Ministry of Health's National Medical Research Council (Singapore Translational Research (STaR) Investigator Award STaR18nov-0002 (D.G.T.); the Singapore Ministry of Education under its Research Centres of Excellence initiative; NIH/NCI Grant R35CA197697 and NIH/NHLBI P01HL131477–01A1 (D.G.T); as well as NIH/NHLBI Grant P01HL095489 and Xiu research fund (L.C.).

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∗ of special interest

∗ ∗ of outstanding interest

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Key Points:

- Aberrantly expressed lncRNAs have prognostic potential and may serve as novel biomarkers for risk stratification in AML.
- Several lncRNAs' expression has been positively correlated with AML chemoresistance, with diverse mechanisms ranging from autophagy regulation to microRNA sponging.
- LncRNAs associated with recurrent mutations in master regulators of hematopoiesis have provided mechanistic insights into their functional roles in AML pathogenesis.

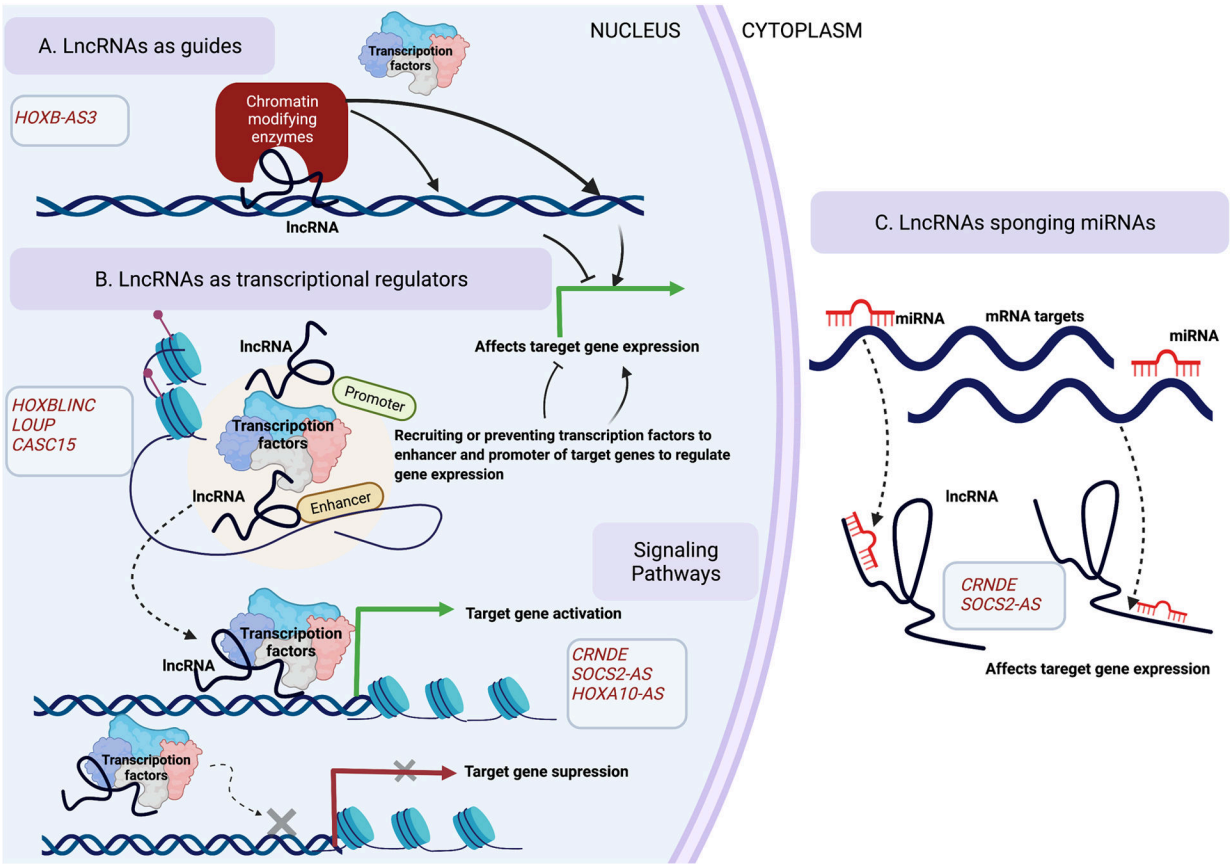

Figure 1. General overview of lncRNA mechanisms involved in AML

(A) LncRNAs can act as a guide to target chromatin-modifying complexes or transcription factors to specific genomic locations and affect the target gene expression. **(B)** LncRNAs can serve as transcriptional regulators that can either recruit or prevent transcriptional factors to the enhancers and promoters of target genes, thereby regulating target gene expression. **(C)** In the cytoplasm, lncRNAs can sequester microRNAs away from their mRNA targets thereby affecting the target gene expression.

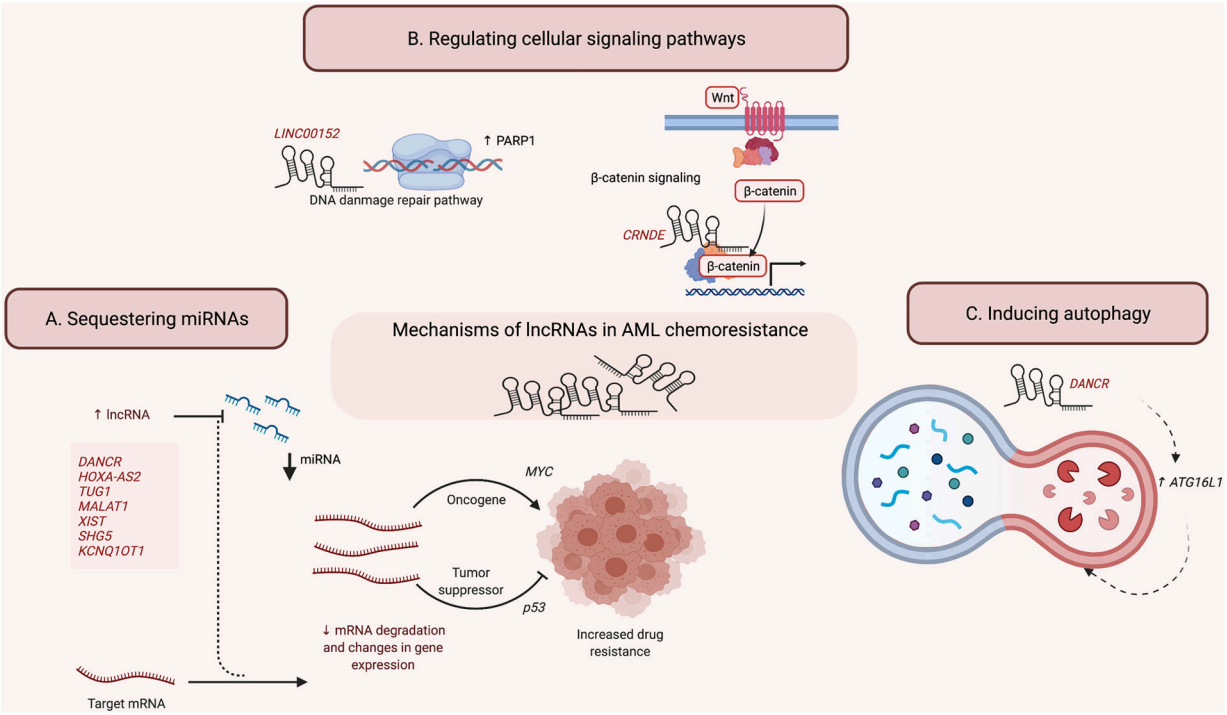

Figure 2. Mechanisms of lncRNAs involved in AML chemoresistance

(A) LncRNAs can sequester miRNAs and affect the expression of downstream oncogenes or tumor suppressors to promote drug resistance. **(B)** LncRNAs can regulate cellular signaling pathways by interacting with transcription factors involved in DNA damage pathways as well as other cell signaling pathways to affect target gene expression. **(C)** LncRNAs can induce autophagy to maintain chemoresistance.

Table 1:

Summary of lncRNAs recently reported in AML

	LncRNAs	Expression in AML	Key findings/mechanism(s) of action	References
LncRNAs associated with *NPM1* mutation	*HOXB-AS3*	upregulated	• Guides EBP1 protein to rDNA locus • Facilitates the interaction of EBP1 with residual NPM1 in nucleolus and maintains adequate amount of rRNA thereby maintaining the proliferative state in leukemic cells by translation of the necessary metabolic proteins	(20)
	HOXBLINC	upregulated	• Overexpression maintains aberrant NPM1c+ signature gene expression program via controlling the MLL1 recruitment • Acts as an epigenetic regulator by remodelling promoter chromatin accessibility in *cis* and *trans* actions	(23)
	LONA	upregulated	• Promotes leukemogenesis via nucleocytoplasmic cross-transport between mutant NPM1 and *LONA* • Modulates key genes involved in myeloid cell differentiation	(26)
	CRNDE	upregulated	• sponges miR-181 and regulates *NOTCH2* in acute promyelocytic cells	(28)
LncRNAs associated with *RUNX1*	*CASC15*	upregulated	• Affects the expression of nearby oncogene-*SOX4* by regulating YY1 transcription factor	(33)
	LOUP	Downregulated in t(8;21) AML patients	• Myeloid specific lncRNA, cooperates with RUNX1 to induce *PU.1* expression thereby promoting myeloid differentiation and inhibiting cell growth • *LOUP* is inhibitory target of RUNX1-ETO in t(8;21) AML	(39)
LncRNAs associated with *FLT3*-ITD, *TET2* mutations	*Morrbid*	Upregulated in AML patients with *FLT3*-ITD, *TET2* mutations	• Loss of *Morrbid* increases expression of Bim which induces apoptosis	(44)
	SOCS2-AS	Upregulated in AML patients with *FLT3*-ITD mutation	• Targets the miR-221/STAT5 signaling pathway	(45)
LncRNAs associated with *MLL*- rearranged leukemia	*LAMP5-AS1*	upregulated	• Maintains high methyltransferase activity of DOT1L thereby upregulating DOT1L target genes	(50)
	HOXA10-AS	upregulated	• HSC-specific lncRNA, acts in *trans* to induce NF-kB target genes	(51)

Table 2:

Recently reported lncRNAs involved in AML chemoresistance

lncRNA	Chemoresistance status	Mechanism of influence	Target	Changes in gene expression	References
DANCR	↑ Chemoresistance to Ara-C	Autophagy, sequestering miRNAs	miR-874–3p	↑ ATG16L1	(55)
LINC00152	LSC chemoresistance	DNA damage repair-related signaling	-	↑ PARP1	(56)
CRNDE	↑ Chemoresistance to ADR	Wnt/β-catenin pathway	-	-	(57)
HOTAIR	↑ Chemoresistance to ADR	AKT/Notch1 signaling pathways	-	↑ p21	(70)
HOXA-AS2	↑ Chemoresistance to ADR	sequestering miRNAs	miR-520c-3p	↑ S100A4	(62)
TUG1	↑ Chemoresistance to ADR	sequestering miRNAs	miR-34a via recruiting EZH2	-	(66)
MALAT1	↑ Chemoresistance to ADR	sequestering miRNAs	miR-96	-	(67)
XIST	↑ Chemoresistance to ADR	sequestering miRNAs	miR-29a	↑ MYC	(69)
SNHG5	↑ Chemoresistance to ADR	Autophagy, sequestering miRNAs	miR-32	↑ DNAJB9	(68)
KCNQ1OT1	↑ Chemoresistance to ADR	sequestering miRNAs	miR-193a-3p	↑ TSPAN-3	(71)